by RAYMOND PARY, MD; PAUL R. MATUSCHKA, PharmD; SUSAN LEWIS, ARNP, PhD; and STEVEN LIPPMANN, MD

Dr. Pary is Staff Psychiatrist; Dr. Matuschka is Clinical Coordinator, Pharmacy Service; and Dr. Lewis is with Mental Health and Behavioral Sciences—All from Veterans Affairs Medical Center, Louisville, Kentucky; Dr. Lippman is with the University of Louisville Hospital in Louisville, Kentucky.

Managing Bipolar Depression

ADDRESS CORRESPONDENCE TO:
Raymond Pary, MD, Staff Psychiatrist, Veterans Affairs Medical Center, 800 Zorn Ave., Louisville, KY 40206
Phone: (502) 287 4011; Fax: (502) 895 6883; E-Mail: raymond.pary@med.va.gov

ABSTRACT

What should the clinician do when confronted with a patient who has depressive symptoms? Seek the proper diagnosis. Question the patient about depressive symptoms over a two-week course that interferes with social and/or occupational functioning. Determine if there is any history of mania or hypomania. Information from a significant other is extremely useful as well. Coexisting diagnoses, such as substance abuse, posttraumatic stress disorder, or medical conditions, must be ruled in or out. It is critical to include a suicide risk assessment in the evaluation. Lithium is still the gold standard for bipolar patients with its suicide preventative effects. Lamotrigine appears to have the advantage of efficacy against bipolar depression without high risk for inducing mania. Experts recommend that a mood stabilizer be used in combination with antidepressants. The tricyclic antidepressants and the monoamine oxidase inhibitors appear to have the highest risk for mania and are best avoided. Atypical antipsychotic medications are best utilized for psychotic symptoms and as adjuncts to existing antidepressants. Cognitive behavioral therapy may complement pharmacotherapy.

INTRODUCTION

Bipolar disorder is a severe neuropsychiatric disorder affecting over 2.3 million American adults, or about one percent of this population.[1] Although therapeutic guidelines for managing mania are consistent, recommendations for treatment of bipolar depression are less clear. Published clinical guidelines often differ from actual practice. Whether or not clinicians should prescribe antidepressant medicines remains controversial. Due to the cyclic nature of bipolar episodes, symptoms can appear to resolve spontaneously. Treatment to achieve a stable mood is crucial because of the high incidence of suicide. Patients with bipolar disorder are at more risk for suicide than patients with any other psychiatric ailment.[2] Untreated bipolar illness can lead to suicide in almost 20 percent of cases.[1]

TABLE 1. Hypothesized abnormalities in bipolar disorder

Kindling hypothesis	**Increasing stress sensitivity and inducing greater episode intensity and lesser wellness intervals over time**
MRI structural changes	**White matter lesions in emotional processing areas of the brain**
Functional changes on PET	**Abnormal brain activity in prefrontal cortex, basal ganglia, and temporal lobes**
Genetic factors	**Unspecified inheritance vulnerabilities**
Neurotransmitter irregularities	**Biogenic amine dysregulation, particularly serotonin and norepinephrine**

Adapted from:

Sadock BJ, Sadock VA. *Mood disorders in Kaplan and Sadock's Synopsis of Psychiatry, Ninth Edition.* Philadelphia, PA: Lippincott Williams & Wilkins. 2003:534–90.

White SH. Mechanism of action of newer anticonvulsants. *J Clin Psychiatry* 2003;64(8): 5–8.

PATHOPHYSIOLOGY

Malfunctions in neurochemistry and activity of brain circuits are responsible for the extreme mood changes, energy levels, and functioning that characterize bipolar disorder. Neuro-imaging studies have verified abnormalities in brain structure and function (Table 1). Magnetic resonance imaging (MRI) has identified the appearance of distinct lesions in the white matter of persons with bipolar disorder. Although pathology is documented in many parts of the brains in people with bipolar illness, they tend to be clustered in areas that are related to emotional processing.[1] These abnormalities appear more often than expected in young patients. Because such white matter lesions do not appear in all bipolar patients and are found in some healthy individuals, their significance is still uncertain.

Positron emission tomography (PET) scans in bipolar patients have identified abnormal activity in various brain areas, including the prefrontal cortex, basal ganglia, and temporal lobes during both manic and depressive episodes. It is still not understood whether these functional changes are a cause or a result of mood disorders.[1]

Bipolar disorder is related to genetic factors although the exact mode of transmission is not understood. Data from family, twin, and adoption studies validate a role of inheritance in bipolar disorder. Researchers are trying to identify genes causing vulnerability to bipolar disorder and the neuroproteins for which they code. This should make it possible to develop better diagnostic procedures and more specific treatments and offer preventative measures focusing on the underlying pathology.[1]

One long-term hypothesis for the etiology of bipolar disorder relates to a kindling model and is analogous to spontaneous seizure induction in animals.[3] Repeatedly inducing an ictus with an electric current eventually results in seizures without such stimulation. Similarly, stress is postulated to alter neural networks over time. The individual becomes increasingly sensitive to psychosocial stressors. Frequent and more intense manic and depressive episodes are elicited with a lesser degree of stress. Unprovoked mood episodes may eventually occur with a shorter interval of wellness.[3]

Mood disorders are associated with heterogeneous dysregulation of the biogenic amines. While serotonin and norepinephrine are the two neurotransmitters most often implicated, it has been suggested that dopamine also plays a role. Researchers have found that dopamine activity may be reduced during a depressive episode.[4]

TABLE 2. Diagnostic features In depression

SYMPTOMS	QUALIFIERS
Depressed mood, most of the day, nearly every day	Either depressed mood or diminished interest must be present
Diminished interest in most activities	Either diminished interest or depressed mood must be present
Significant weight loss or gain or change in appetite	A change of more than 5% of body weight in a month is significant
Insomnia or hypersomnia nearly every day	A change from previous sleep patterns should be noted
Psychomotor agitation or retardation	This should be observable and verifiable by others
Fatigue or loss of energy	Daily complaints qualify this for a criterion
Feelings of worthlessness or guilt nearly every day	More than mild self reproach about being sick is necessary
Diminished concentration or indecisiveness	This symptom can be by subjective or objective
Recurrent thoughts of death, recurrent suicidal ideation, either a suicidal attempt or a specific plan to commit suicide	More specific ideation than just a fear of dying is necessary
Five of nine symptoms are present during a two-week period	A change from previous functioning must occur

Adapted from:
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.* Washington, DC: American Psychiatric Association; 2000:356.

DIAGNOSIS

Bipolar depression is challenging even to the most skilled clinician. An individual who manifests a depressive condition can be suffering from a major depressive disorder (Table 2), bipolar disorder, or substance-induced depressive symptoms (Table 3). In order to classify these conditions properly, a history of mania or hypomania must be established for a bipolar disorder diagnosis or excluded for major depression (Table 4). A substance abuse history must be explored as well. Distinguishing the separate illnesses causing depression can be verified by also taking a history from a significant other. Reviewing collateral information from hospital records is helpful as well. It is often difficult to make an adequate bipolar disorder diagnosis through interviewing only the patient.

People experiencing a depressive illness must exhibit a depressed mood for most of the day, nearly every day for at least a two-week period (Table 2).[4] Other typical symptoms include diminished interest or pleasure, weight changes, insomnia, and poor concentration. Feelings of worthlessness, fatigue, and agitation may occur as well. Recurrent thoughts of death or suicidal preoccupation are frequent; generally the person has marked functional impairment and is clinically distressed. Five symptoms are required during the two-week period for a diagnosis of depression.

A patient with bipolar depression has had a depressive period and a previous hypomanic or manic episode. Individuals may not complain of mood elevations since they experience them as periods of increased productivity and energy, which can make obtaining an accurate history of hypomania or mania difficult to establish.

It is important for physicians to ask about previous mood swings. A mood disorder questionnaire can help structure this type of questioning.[6] Questions regarding different types of mood, such as feeling good and getting into trouble, not missing lost sleep, speaking faster than usual, and having racing thoughts, are necessary. Other screening questions focus on increased energy, excessive activity, unusual social calls late at night, frivolous spending tendencies, and risky financial management. Excessive or uncharacteristic sexual behavior should also be queried.

One key concept in eliciting a previous manic or hypomanic episode is symptom clustering. Physicians should inquire about events and/or symptoms that occurred during a specific period of time. Other critical issues concern the degree of interference in the patient's routine life. Individuals with disordered mood often have involvement with legal authorities, difficulties within their families, and/or problems at work.

TABLE 3. Diagnostic issues in bipolar disorder

Major depressive disorder	History of mania excluded
Bipolar disorder, most recently depressed	History of mania verified
Substance induced mood disorder with depressive features	Depression a probable consequence of substance abuse
Previous manic episode	Typically associated with the individual getting into trouble and symptom clustering
Feeling good as part of normal mood range	The individual stays out of trouble and is functional and productive
Recognition of previous manic episode	History from significant other or evidence of mania in past medical records

Adapted from:
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.* Washington, DC: American Psychiatric Association; 2000:345–428

Mania causes a major impairment in occupational or social functioning and most cases require hospitalization.[7] Hypomania does not usually necessitate hospitalization but results in uncharacteristic behavior that is noticeable by others for several days.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of bipolar disorder includes a wide variety of medical and psychiatric illnesses. Major depressive or schizoaffective disorder, substance abuse, personality disorders, and posttraumatic stress disorder may mimic a bipolar pattern. Coexistence of such syndromes with bipolar disorder is possible as well. Thyroid pathology, seizure disorders, and steroid-induced mood symptoms are among the leading medical conditions that should be eliminated in a person presenting with a mood disorder.

EVALUATION

A complete medical and psychiatric history is the cornerstone of good practice. Areas for concentration during the physical examination would be the endocrine system and signs of alcohol or other substance abuse. As indicated, laboratory testing may include the thyroid stimulating hormone, a toxicology screen, an electroencephalogram, or brain imaging. Primary care providers often see patients who report symptoms of depression. It is not uncommon for bipolar patients to seek treatment when they are depressed rather than manic or hypomanic. Some physicians recommend that anyone with depressive symptoms be evaluated for bipolar depression.[7,8] Screening tools for bipolar disorder may be used to alert clinicians to the possibility of bipolar spectrum disorders; however, it is crucial to remember that these tools are not diagnostic, but merely clues that further evaluation is needed.

In office settings, the Mood Disorder Questionnaire (MDQ), a screening inventory for bipolar I and bipolar II disorders, has been used as a simple guideline for improving recognition of bipolar disorder.[8,9] The MDQ is a 15-item self-report of lifetime bipolar symptoms based on DSM IV criteria that has been validated in a US multicenter study.[9,10] It can be used to identify patients who have past or present mania/ hypomania and may have bipolar spectrum disorders.[7] The accuracy and usefulness of the MDQ has been questioned, and is felt by some researchers to perform moderately.[11] The initial studies were performed in academic settings with patients already being treated for bipolar disorder. It was felt that one of the problems with the MDQ was that the scale was not sufficiently sensitive to be used for case-finding in community settings or as a screening scale in clinical practice. In addition, it was not as responsive in identifying milder bipolar spectrum disorders as opposed to bipolar I disorder.[11]

Nothing substitutes for a thorough history and clinical assessment in making a diagnosis of bipolar disorder. Eliciting information relevant to bipolar disorder from the patient and his family is essential. The patient should be questioned about the age of onset of mood symptoms, if mood changes occur abruptly or slowly, previous problems with antidepressants, and history of hypomanic or manic episodes.[7] The importance of ruling out bipolar disorder cannot be stressed enough. If the patient is incorrectly diagnosed with unipolar depression and given standard antidepressant therapy, it can result in precipitating a major episode.

COURSE

Individuals with bipolar disorder most commonly suffer

relapses and remissions. Approximately 90 percent of them have had a psychiatric hospitalization. During their lifetimes most have multiple admissions for a bipolar episode.[12] Bipolar II patients are more likely to present with depression than with hypomania or mania.[13] Comorbid substance abuse is common.[14]

TREATMENT

Patients should be treated with psychological interventions in addition to drug therapy (Table 5). Education and a therapeutic relationship with treatment staff may prevent bipolar relapse, improve adherence, and promote early symptom recognition.

When a bipolar patient experiences breakthrough depressive symptoms, this may indicate recurrent bipolar depression or development of a mixed episode.[15] Management of these conditions differs. Mood prior to a breakthrough depressive episode appears to be related to the effectiveness of either antidepressant or mood stabilizer medications.[15]

Individuals should be encouraged to monitor their feelings and alterations of usual routines daily. Relatives and patients should be aware of typical warning signs of new episodes. They can be taught to be aware of mood changes, appetite or sleep alterations, increases in anxiety, and shifts in activity.[2] Most persons can often recognize prodromal symptoms (e.g., changes in mood, appetite, sleep patterns, anxiety, activity, and energy) prior to onset of a depressive episode.[2] It is important to ask patients about their feelings before their depression started. Relatives or significant others should be questioned about mood changes before or immediately after previous depressive episodes.

Cognitive therapy has been shown to prevent bipolar relapse in a controlled investigation.[16] Compared with controls, fewer of those receiving cognitive therapy experienced a relapse, while treatment adherence and social functioning improved. Instructions promoting good sleep hygiene and the necessity for treatment adherence are beneficial.

Bipolar disorder is a lifelong illness. Consequently, treatment of the acute episode requires consideration of its pharmacological effects over the entire course of the disorder. Antidepressant monotherapy is less effective in preventing breakthrough depression than an antidepressant and mood stabilizer combination.[17] The use of an antidepressant medicine without a coprescribed drug to provide mood stability may worsen the overall course of bipolar illness.

Subclinical symptoms of depression commonly emerge between manic episodes.[18] This can impair an individual's ability to function and compromises overall quality of life. Risk for a full relapse is increased; an aggressive treatment approach is warranted.

PHARMACOLOGY

Lithium has been the standard of treatment for bipolar disorders and is effective both in reducing manic symptoms as well as in preventing future episodes. A literature review of acute bipolar depression found lithium to be efficacious; however, much of the early research tended to be poorly designed.[19]

The possibility of a bipolar depressed patient progressing into mania, hypomania, or rapid cycling is a concern. Lithium is associated with the lowest rate of such mood switching.[19] One long-term investigation revealed that

TABLE 4. Diagnostic features in hypomania

SYMPTOMS	QUALIFIERS
Inflated self esteem	Occurs usually at the level of uncritical self confidence
Decreased need for sleep	Feels rested after minimal sleep
More talkative than usual	Speech may be rapid and pressured.
Racing thoughts	May include flight of ideas
Increase in goal-directed activity	Social, occupational, or sexual behaviors are increased
Poor judgment regarding high risk situations	Buying sprees, legal difficulties, or unwise investments are typical
Distractibility	Attends often to trivial stimuli
An episode of persistently elevated, expansive, or irritable mood	Four-day duration with a distinct functional change must occur

Adapted from:
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.* Washington, DC: American Psychiatric Association; 2000:365–68

about one third of bipolar subjects on lithium monotherapy remain totally free of affective episodes over a 10-year period.[20] If a patient experiences a breakthrough depression while taking lithium, one strategy is to increase the lithium dose to achieve a high-normal therapeutic level.[15]

Lithium is recommended as a preventive measure.[2] Discontinuing or switching lithium to a different mood stabilizer should only be done with caution, because lithium has protective effects against suicidal tendencies, even though the response may have been otherwise suboptimal.[21] In a review of 5,647 subjects included in 22 investigations, suicide was 82-percent less frequent for patients prescribed lithium as compared to those not receiving lithium.[22] Another report indicated that patients treated with lithium have a lower risk for suicide than those treated with divalproex.[23] In summary, research has shown lithium to be effective in decreasing suicidal behavior in bipolar disorder (Table 6).[21] Appropriate, early treatment can greatly reduce suicide rates in such individuals.

A controlled study of gabapentin, lamotrigine, and placebo monotherapy in refractory mood disorders found that 26 percent of depressed patients responded to gabapentin.[24] This compared with improvement in depression scores for those taking lamotrigine at 45 percent and for placebo at 19 percent. Used alone, gabapentin would be insufficient treatment for bipolar depression. Lamotrigine was the most effective for such depressions.

An open-label study examined the effects of gabapentin as adjunctive medication in people with mixed manic and depressive symptoms.[25] Rapid reductions in insomnia were observed and go along with improved ratings for depression and mania.

TABLE 5. Interventions in bipolar depression

ESTABLISHING AND MAINTAINING A THERAPEUTIC RELATIONSHIP	THE CORNERSTONE OF ALL TREATMENT
Instructions to patient	Patient to be aware of mood changes, appetite and sleep alterations, and shifts in activity
Typical early warning signs of depression	Indecisiveness and lapses in attentiveness
Instructions to family	Family to be aware of individualized early symptoms prodromal for depression
Education to family and patient	Treatment compliance important with illness relapse expected

Adapted from:

Bowden CL Managing bipolar depression. *J Clin Psychiatry* 2004:65(10):3–4.

American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 2002;159(4):1–50.

Lamotrigine has received approval from the US Food and Drug Administration (FDA) for maintenance treatment in bipolar disorder. There is differential effectiveness depending on the patient's presenting type of mood disorder. For mania, only one of four double-blind studies gave this drug a favorable rating over placebo.[26] Better efficacy was apparent when lamotrigine was utilized for cases with depression.

In a double-blind, placebo-controlled trial of acute bipolar depressed subjects, those receiving lamotrigine, 200mg daily, improved significantly on all criteria, and these were noted as early as the third week of therapy.[27] Subsequently, lamotrigine and lithium were compared in an 18-month maintenance trial by the same investigators.[28] Compared to placebo, lamotrigine was more effective at delaying depressive episodes while lithium was predominantly effective against mania.

Lamotrigine has also proved superior to both placebo and gabapentin in another investigation.[24] Lamotrigine might be particularly effective in combating rapid cycling depressive relapse in bipolar II patients.

Antidepressant/lithium combination therapies have been studied. A double-blind comparison was made of imipramine/lithium, paroxetine/lithium, and placebo/lithium combinations.[29] For those subjects with lithium levels greater than 0.8mEq/L, there were no differences between the three treatment groups. For groups who had lithium levels below 0.4mEq/L, the imipramine/lithium and paroxetine/lithium ones evidenced greater benefit than for placebo/lithium.

Olanzapine and an olanzapine/fluoxetine strategy have demonstrated advantageous effects for bipolar depression.[30]

The olanzapine/fluoxetine combination had the best response and remission. It was more effective than olanzapine alone or the placebo. The rates of treatment-emergent mania were low in all three groups.

It is currently unknown if risperidone, aripiprazole, and ziprasidone have efficacy for treating acute bipolar depression.[31] Aripiprazole and quetiapine may have antidepressant properties but more data is needed regarding both drugs. However, overall the atypical antipsychotic drugs should be considered for adjunctive treatment to existing antidepressant armamentarium in bipolar disorder.

Valproate products have proven efficacy for mania, but their effectiveness against moderate to severe depressive episodes is substantially less robust.[32] A moderate degree of acute or prophylactic efficacy has been demonstrated with carbamazepine in bipolar depression.[33,34] There is only one published placebo-controlled monotherapy trial of this drug for bipolar depression, however.[32]

When used as maintenance treatment for bipolar disorder, carbamazepine and valproate have greater efficacy when used in combinations.[35] Examples would include carbamazepine and lithium and valproate and olanzapine. Prevention of relapse and recurrence of bipolar disorder would thereby be enhanced.

Clozaril has been found to have mood stabilizing properties in people with treatment-resistant illness and a history of mania.[36] When used as monotherapy, it has been useful as well in bipolar patients with psychotic features.[37]

TABLE 6. Features of drugs in bipolar depression

Lithium	**Reduced likelihood of suicide with some effectiveness for bipolar depression**
Lamotrigine	**Effective for bipolar depression**
Carbamazepine	**Doubtful efficacy for bipolar depression**
Valproate	**Doubtful efficacy for bipolar depression**
Selective serotonin reuptake inhibitor antidepressant/mood stabilizer combination	**Effective in bipolar depression, but controversial risk for mania in rapid cycling patients**
Tricyclic antidepressants/MAOIs	**High risk for induction of mania**
Olanzapine/fluoxetine	**Effective for bipolar depression**

Adapted from:
American Psychiatric Association: Practice Guideline for the Treatment of Patients with Bipolar Disorder (Revision). *Am J Psychiatry* 2002; 159(4): 1–50.

Since clozapine therapy involves the possibility of agranulocytosis, weight gain, and increased risk for diabetes, it is a reasonable consideration only for the more severe treatment-resistant cases. Such individuals should accept the necessary close blood monitoring and be capable of treatment adherence over the long term. Discontinuation of this drug or any of the atypical antipsychotic medications that cause excessive weight gain or hyperglycemia may be necessary. An internal medicine consult request would be an additional strategy to manage significant adverse side effects from these compounds.

An international consensus group on the treatment of bipolar depression gave specific recommendations for depressed, nonresponding patients.[38] Adding a selective serotonin reuptake inhibitor (SSRI) to either lithium or lamotrigine can treat those without a history of rapid cycling (four episodes of either mania or depression in a year). An alternative method would be to combine lithium with lamotrigine. They also endorsed the lithium/olanzapine/fluoxetine combination.

Augmentation strategies for treatment-resistant depression have included the addition of thyroid hormone. In a review of antidepressant supplementation, usually utilizing triiodothyronine in dosages of 25 to 50mcg/day, significant effect was observed in about half of the published studies.[39] This strategy may be favored for patients with hypothyroid indices and residual fatigue.[40]

Stimulants have been utilized in depression. Fatigue has been treated with modafinil added to an existing antidepressant. Improvement of sleepiness and fatigue has been noted in depressed patients.[41,42] Case reports of augmentation of venlafaxine and citalopram with

TABLE 7. Medications in bipolar depression

MEDICATION (DOSE RANGE)	COMMENTS
Aripiprazole (15–30mg)	No adverse metabolic effects have been seen. Lack of sedation mandates morning administration. FDA approved for bipolar disorder.
Carbamazepine (Dose based on blood levels)	Serum level 4–12mcg/mL; Numerous drug-drug interactions. FDA approved for bipolar disorder.
Citalopram (20–60mg)	Not FDA approved for bipolar disorder.
Escitalopram (10–20mg)	Not FDA approved for bipolar disorder.
Fluoxetine (10–80mg)	Not FDA approved for bipolar disorder.
Gabapentin (300–3600mg)	Not FDA approved for bipolar disorder.
Lamotrigine (200–400mg)	Slow dose titration is warranted due to risk of Stevens-Johnson syndrome with rapid dose increases. FDA approved for bipolar disorder.
Levetiracetam (1000–3000mg)	Dose must be adjusted for renal insufficiency. Not FDA approved for bipolar disorder. Not yet satisfactorily tested in adequate trials for bipolar disorder. Case report or open label studies only.
Lithium (Dose based on blood level)	Acute 1–1.5mmol/L; Maintenance 0.6–1.2mmol/L; Monitor renal function. FDA approved for bipolar disorder.
Olanzapine (2.5–20mg)	Monitor for adverse metabolic effects including weight gain, hyperglycemia, and lipid abnormalities. FDA approved for bipolar disorder.
Olanzapine/fluoxetine(6/25–18/75mg)	Same as for olanzapine.
Oxcarbazepine (600–2400mg)	Serious skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred. Not FDA approved for bipolar disorder. Studied primarily in acute mania.
Paroxetine (10–60mg)	FDA warning on birth defects; use with caution in women of child-bearing age. FDA approved for bipolar disorder.
Quetiapine (400–800mg)	Monitor for adverse metabolic effects including weight gain, hyperglycemia, and lipid abnormalities. FDA approved for bipolar disorder.
Risperidone (1–6mg)	FDA approved in bipolar disorder.
Sertraline (25–200mg)	Not FDA approved in bipolar disorder.
Topiramate (100–400mg)	Therapy should be initiated at 25–50mg/day followed by titration to an effective dose in increments of no more than 25mg/day on a weekly basis. Not FDA approved for bipolar disorder. Placebo-controlled studies attesting efficacy in bipolar depression are lacking. Generally ineffective in controlled trials for bipolar disorder.
Valproate (Dose based on blood levels)	50–125mcg/mL. For once daily dosing use 60mg/kg; Numerous drug-drug interactions. FDA approved for bipolar disorder disorder.
Ziprasidone (80–160mg)	Food doubles the amount of ziprasidone absorbed after oral dosing; therefore, give with meals. FDA approved for bipolar disorder.

Adapted from:
DRUGDEX® System. Thomson Micromedex, Greenwood Village, Colorado Healthcare Series, 2005;125.
Bowden CI. Acute and maintenance treatment with mood stabilizers. *Internat J Neuropsychopharmacol* 2003;6: 269–75.
Yatham LN. Newer anticonvulsants in the treatment of bipolar disorder. *J Clin Psychiatry* 2004; 65 (suppl 10): 28-35.

methylphenidate have been favorable in a refractory elderly depressed population.[43,44] In another report, acute symptomatic improvement after d-amphetamine or methylphenidate was unpredictable in a group of depressed inpatients.[45] Either stimulant can be tried if the other is not helpful. The long-term benefits of selective stimulant therapy have yet to be assessed, however. Patients with bipolar depression who are receiving augmentation strategies should also receive a mood stabilizer.

Additionally, these experts discussed the antidepressant drugs that are most likely to cause mania. The tricyclics (TCAs) and the monoamine oxidase inhibitors (MAOIs) were most known to induce manic switches; therefore, these pharmaceuticals are best avoided.[38]

A review of available clinical trial data was conducted on the rates of treatment-emergent switch into mania associated with SSRIs, TCAs, and placebo use.[46] Data on bipolar depressive persons treated with SSRIs related in this assessment primarily to sertraline and paroxetine.[46] A 3.7-percent switch rate into mania occurs for the SSRIs.[46] This compares to 4.2-percent rate from placebo and contrasts with an 11.2-percent occurrence for TCAs. Therefore, patients at risk for antidepressant-induced mania might best be treated with SSRIs rather than TCAs. Another article reviewed the data for switches into mania, and it reported manic induction associated with SSRIs and lamotrigine as similar to placebo rates.[47] Many clinicians try to avoid the use of antidepressant drugs if possible in bipolar patients.

For treatment-unresponsive, rapid-cycling patients with depressive symptoms, the international consensus group recommends adding either a valproate product or olanzapine to lithium.[38] Depressed people who are taking two mood stabilizers or one mood stabilizer with olanzapine can be tried on an SSRI, if indicated. If the patient is psychotic, olanzapine has been recommended.[32] With further investigations, though, the second generation antipsychotic drugs, as a class should also be effective.

ECT is effective for bipolar depression with better results than most pharmacological therapies.[19,48] ECT is especially useful for those with a high risk of suicide, psychomotor retardation, or treatment resistance with psychosis.[49,50] Although transcranial stimulation (TMS) has been proposed as a treatment for depression, there is no strong evidence for benefit from using this modality to treat depression. Numbers of subjects used in TMS investigations have been small. The possibility of some symptomatic help from TMS is not excluded, however.

Vagus nerve stimulation (VNS) may be useful for treatment-resistant bipolar depressed patients. In a naturalistic pilot study, adjunctive VNS demonstrated a sustained antidepressant response over a two-year period.[51] All patients were depressed and resistant to treatment, with some subjects having bipolar depression. This treatment was well tolerated and exhibited a low attrition rate.

Cingulotomy can be helpful in patients with severe, disabling, and treatment-refractory major affective disorder.[52] Complications from this MRI-guided stereotactic technique are few, with some patients being considerably improved. It is usually reserved for patients who have tried and repeatedly failed less intrusive treatment and are willing and capable of giving informed consent. A multidisciplinary team approach is essential for this procedure.

Evaluating the severity of a previous manic episode before adding antidepressant treatment has been a recommended strategy by some authorities. According to one expert,[53] patients who have a manic history that involved either self harm or damage to the family should not be given antidepressants. However, if the mania was moderate without hurt

THE PRIMARY GOAL [of bipolar disorder treatment] should be managing the disease itself and not merely the acute episodes of mania or depression.

TRADE NAME DRUG KEY

ARIPIPRAZOLE—Abilify®

CARBAMAZEPINE—Biston®; Calepsin®; Carbatrol®; Epitol®; Finlepsin®; Sirtal®; Stazepine®; Tegretol®; Telesmin®; Timonil®

CITALOPRAM—Celexa™; Cipramil™

ESCITALOPRAM—Lexapro™; Cipralex™

FLUOXETINE—Prozac®

GABAPENTIN—Neurontin®

LAMOTRIGINE—Lamictal®

LEVETIRACETAM—Keppra®

OLANZAPINE—Zyprexa®

OLANZAPINE/FLUOXETINE—Symbyax®

OXCARBAZEPINE—Trileptal®

PAROXETINE—Paxil®

QUETIAPINE—Seroquel®

RISPERIDONE—Belivon®; Rispen®; Risperdal®

SERTRALINE—Zoloft®; Lustral®; Apo-Sertral®; Asentra®; Gladem®; Serlift®; Stimuloton®

TOPIRAMATE—Topamax®

VALPROATE—Depakote®

ZIPRASIDONE—Geodon®

or injury, antidepressants should be added to a mood stabilizer to treat depression.

Alternative viewpoints regarding the safety of SSRIs have also been published. In a recent systematic review of randomized, controlled trials of antidepressant drugs for bipolar depression, disagreements with the existing American Psychiatric Association's practice guidelines for the treatment of bipolar disorder were as follows: 1) There are no compelling reasons to avoid antidepressants.[54] This is at variance with the recommendation to use lithium or lamotrigine as a first-line treatment for bipolar depression; 2) Bipolar-depressed patients who are already taking a mood stabilizer should receive an antidepressant medication adjunctively. For individuals with a history of mania who are not on a mood stabilizer, the prescription of a mood stabilizer with an antidepressant is warranted.

The optimal length of time to continue an antidepressant drug is also controversial. In bipolar patients who respond favorably to an antidepressant, a recent report favors continuance of the antidepressant after remission. Those who had bipolar depressive remissions on an antidepressant and mood stabilizer medicine were followed for a year.[55] The risk of relapse into depression was higher for patients who stopped medication within six months of remission than in persons who discontinued pharmacotherapy more than six months after recovery.

CONCLUSION

Bipolar disorder is a chronic condition requiring treatment throughout a lifetime. The primary goal should be managing the disease itself and not merely the acute episodes of mania or depression. There is no consensus on the proper pharmacological management for bipolar depression. Lithium and lamotrigine have been beneficial in acute bipolar depression and are commonly selected in such circumstances. The combination of a mood stabilizer and an SSRI antidepressant drug has so far shown to be a reasonable other choice for bipolar depression. Prescribing lithium and/or lamotrigine for depression in bipolar patient is recommended as a first-line pharmacotherapy. Monotherapy with an antidepressant is generally avoided. The addition of antipsychotic medications may also be warranted. Long-term safety outcomes, efficacy of medications, use of ECT, and psychosocial treatment modalities should all be considered for these patients' improved quality of life.

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EDITOR'S NOTE

DEAR READERS:

Since this article was written and submitted for peer review, the results from the BOLDER II (BipOLar DEpRession) study have been released. In BOLDER II, SEROQUEL® (quetiapine) 300mg and 600mg doses achieved a statistically significant reduction in levels of bipolar depression compared with placebo ($p<0.001$), as measured by the change from baseline in MADRS total score. This was true for patients with both bipolar I and bipolar II disorders. These confirm the results of the BOLDER I[1] study, which was very similar in design. This is the first time an atypical antipsychotic has been shown in large studies to be effective as monotherapy for bipolar depression.

Based on these results, AstraZeneca is seeking a new FDA indication for SEROQUEL for the treatment of patients with depressive episodes associated with bipolar disorder. It will be interesting to see if these results are replicated by some of the other second generation antipsychotics.

With regards,
Amir Kalali, MD
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